National HIV Curriculum

Mini-Lecture Series

Long-Acting, Injectable Cabotegravir-Rilpivirine

Brian R. Wood, MD
Associate Editor, National HIV Curriculum
Associate Professor of Medicine
Division of Allergy and Infectious Diseases
University of Washington

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AETC Program

Disclosures

Dr. Wood has no financial conflicts of interest or disclosures.

Cabotegravir and Rilpivirine
Oral and Injectable Preparations

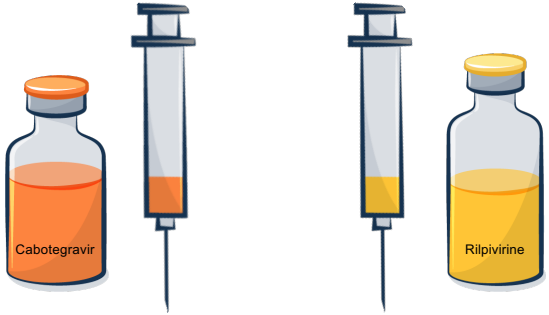
Optional Lead-In Oral Components

Cabotegravir + Rilpivirine

30 mg → INSTI

25 mg → NNRTI

Intramuscular Injection Components



Cabotegravir + Rilpivirine

200 mg/mL → INSTI

300 mg/mL → NNRTI

Cabotegravir and Rilpivirine Extended Release Injectable Suspension Indications

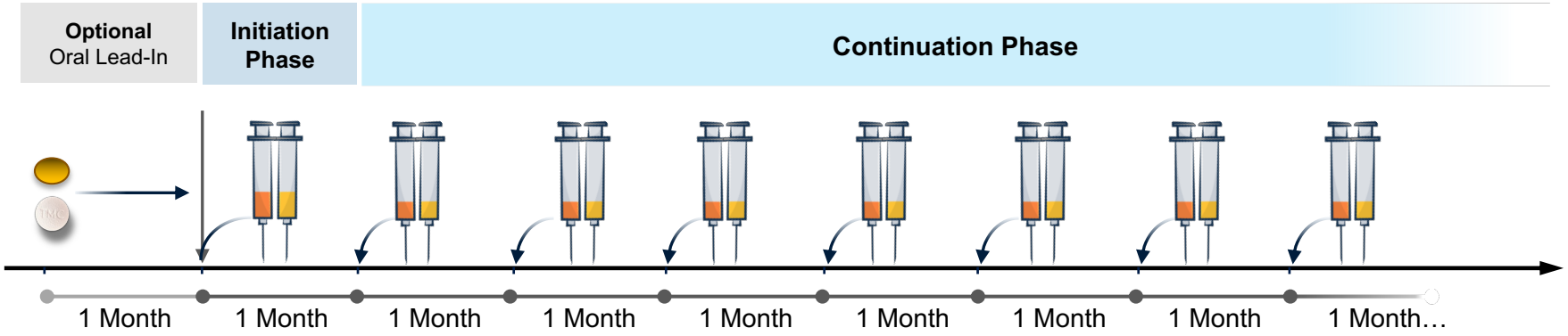
- **Complete regimen to treat HIV-1**
- **For adults and adolescents (≥12 years who weigh ≥35 kg)**
  - Replace antiretroviral regimen in persons with HIV RNA <50 copies/mL
  - On stable antiretroviral regimen
  - No history of treatment failure
  - No known or suspected resistance to cabotegravir or rilpivirine
- **Oral Lead-In**
  - Lead-in is optional
- **Continuation Phase Injections**
  - Approved for every 1-month and every 2-month injections
  - Doses are different with every 1-month and every 2-month injections
  - Injections may be given up to 7 days before or after the scheduled date

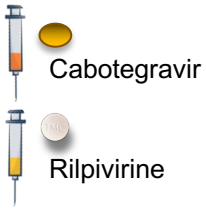
Source: Cabotegravir-Rilpivirine Prescribing Information

Schedule for Every 1-Month Injectable Cabotegravir and Rilpivirine

Schedule for Injections*: One-time initiation phase injections then monthly continuation phase injections thereafter

Administer first injections on the last day of current fully suppressive antiretroviral therapy or last day of oral lead-in (if used)





Optional Oral Lead-In Dosing: Cabotegravir 30 mg PO daily and Rilpivirine 25 mg PO daily

***Dosing for 1-time Initiation Phase Injections** = LA Cabotegravir (600 mg): 3 mL IM and Rilpivirine (900 mg): 3 mL IM

***Dosing for Continuation Phase Injections** = LA Cabotegravir (400 mg): 2 mL IM and Rilpivirine (600 mg): 2 mL IM

Injections of rilpivirine and cabotegravir given as 2 separate IM injections at separate gluteal sites (opposite sites or 2 cm apart on same site)
Injections may be given up to 7 days before or after the scheduled date

Source: Cabotegravir-Rilpivirine Prescribing Information; Illustration: David H. Spach, MD

Management of Missed Injections in Persons on Every 1-Month Dosing

Management for Planned and Unplanned Missed Injections in Patients on Every 1-Month Dosing

Time Since Last Injection	Recommendation for Oral Bridging
Planned Missed Injection • Time to miss a scheduled injection >7 days	• **Two oral options are are available**: - Take daily oral therapy with cabotegravir 30 mg plus rilpivirine 25 mg for up to 2 months to replace missed injection visits. - Take any fully suppressive antiretroviral regimen until injections resume • Start oral therapy with either option above approximately 1 month (+/- 7 days) after the last injection dose of cabotegravir and rilpivirine. • Continue oral therapy until the day injection dosing is restarted.
Unplanned Missed Injection • Time from last injections is >1 month + 7 days	• If oral therapy has not been taken, reassess patients clinically to ensure resumption of injections remains appropriate.

Source: Cabotegravir-Rilpivirine Prescribing Information

Recommendations for Restarting Injection Doses after Missed Injections with Every 1-Month Dosing Schedule

Injection Dosing Recommendations after Missed Injections with Every-1-Month Dosing Schedule	
Time Since Last Injection	**Recommendation**
Less than or equal to 2 months	Resume with cabotegravir 400 mg (2 mL) and rilpivirine 600 mg (2 mL) monthly injections as soon as possible.
Greater than 2 months	Reinitiate with with cabotegravir 600 mg (3 mL) and rilpivirine 900 mg (3 mL) then continue to follow the monthly cabotegravir 400 mg (2 mL) and rilpivirine 600 mg (2 mL) monthly injection dosing schedule.

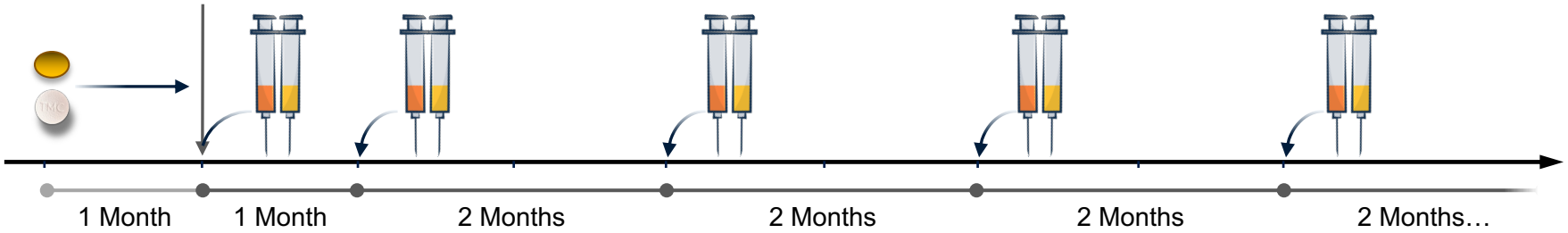
Source: Cabotegravir-Rilpivirine Prescribing Information

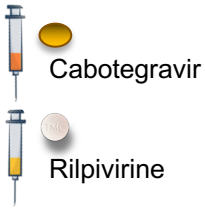
Schedule for Every 2-Month Injectable Cabotegravir and Rilpivirine

Schedule for Injections*: First two injections given 1 month apart then every 2 months thereafter

Administer first injections on the last day of current antiretroviral therapy or last day of oral lead-in (if used)

Optional Oral Lead-In	**Initiation Phase**	**Continuation Phase**





Optional Oral Lead-In Dosing: Cabotegravir 30 mg PO daily and Rilpivirine 25 mg PO daily

***First Two Injections (Initiation Phase):** given 1 month apart, before transitioning to every 2-month dosing

***Dosing for All Injections** = LA Cabotegravir (600 mg): 3 mL IM and Rilpivirine (900 mg): 3 mL IM

Injections of rilpivirine and cabotegravir given as 2 separate IM injections at separate gluteal sites (opposite sites or 2 cm apart on same site)
Injections may be given up to 7 days before or after the scheduled date

Source: Cabotegravir-Rilpivirine Prescribing Information; Illustration: David H. Spach, MD

Management of Missed Injections in Persons on Every 2-Month Dosing

Oral Bridge Therapy for Planned and Unplanned Missed Injections in Patients on 2-Month Dosing

Time Since Last Injection	Recommendation for Oral Bridging
Planned Missed Injection • Time to miss a scheduled injection >7 days	• **Two oral options are are available**: - Take daily oral therapy with cabotegravir 50 mg plus rilpivirine 25 mg for up to 2 months to replace missed injection visits. - Take any fully suppressive antiretroviral regimen until injections resume • Start oral therapy with either option above approximately 2 months (+/- 7 days) after the last injection doses. • Continue oral therapy until the day injection dosing is restarted.
Unplanned Missed Injection • Time for scheduled injection is missed or delayed by >7 days	• If oral therapy has not been taken, reassess patients clinically to ensure resumption of injections remains appropriate.

Source: Cabotegravir-Rilpivirine Prescribing Information

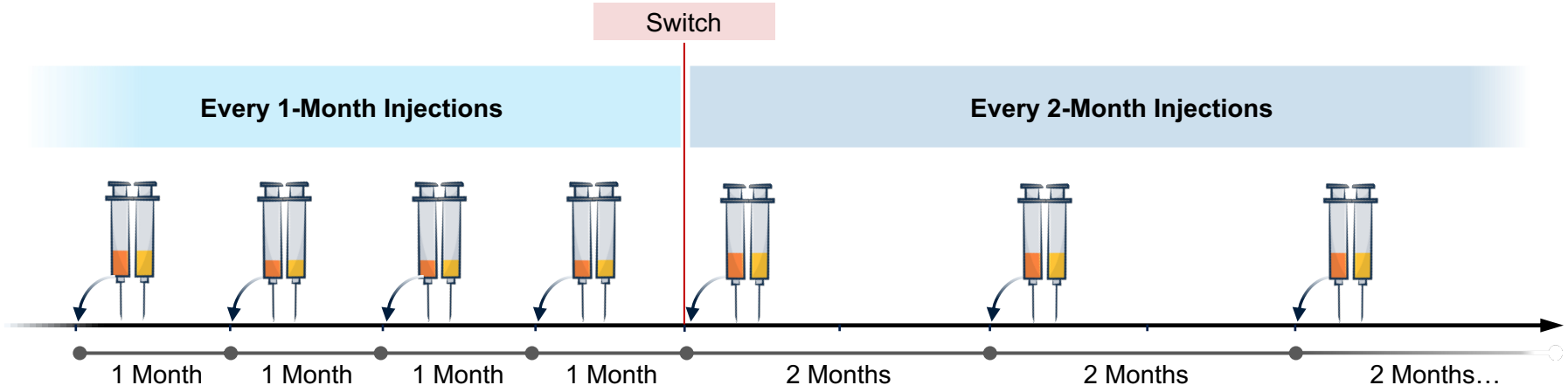
Recommendations for Restarting Injection Doses after Missed Injections with Every 2-Month Dosing Schedule

Injection Dosing Recommendations after Missed Injections with Every-2-Month Dosing Schedule

Missed Injection Visit	Recommendation
Injection 2	• **Time since last injection ≤2 months**: Resume with cabotegravir 600 mg (3 mL) and rilpivirine 900 mg (3 mL) as soon as possible, then continue to follow the every-2-month injection dosing schedule. • **Time since last injection >2 months**: Re-initiate the patient with cabotegravir 600 mg (3 mL) and rilpivirine 900 mg (3 mL) followed by the second initiation injection dose 1 month later. Then continue to follow the every-2-month injection dosing schedule thereafter.
Injection 3 or Later	• **Time since last injection ≤3 months**: Resume with cabotegravir 600 mg (3 mL) and rilpivirine 900 mg (3 mL) as soon as possible and continue with the every-2-month injection dosing schedule. • **Time since last injection >3 months**: Re-initiate the patient with cabotegravir 600 mg (3 mL) and rilpivirine 900 mg (3 mL) followed by the second initiation injection dose 1 month later. Then continue with the every-2-month injection dosing schedule thereafter.

Source: Cabotegravir-Rilpivirine Prescribing Information

Cabotegravir and Rilpivirine Extended-Release Injectable Suspension
Switching from Every 1-Month to Every 2-Month Cabotegravir and Rilpivirine



Cabotegravir

Rilpivirine

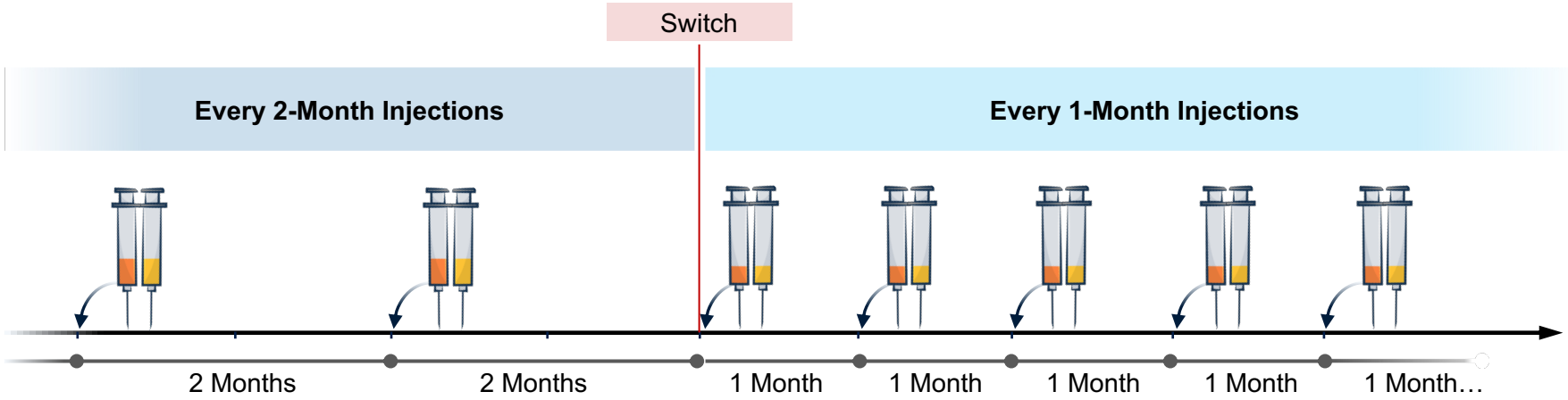
*__Dosing for Every 1-Month Injections__ = LA Cabotegravir (400 mg): 2 mL IM and Rilpivirine (600 mg): 2 mL IM

*__Dosing for Every 2-Month Injections__ = LA Cabotegravir (600 mg): 3 mL IM and Rilpivirine (900 mg): 3 mL IM

Injections of rilpivirine and cabotegravir given as 2 separate IM injections at separate gluteal sites (opposite sites or 2 cm apart on same site)

Source: Cabotegravir-Rilpivirine Prescribing Information; Illustration: David H. Spach, MD

Cabotegravir and Rilpivirine Extended-Release Injectable Suspension
Switching from Every 2-Month to Every 1-Month Cabotegravir and Rilpivirine



Cabotegravir

Rilpivirine

*__Dosing for Every 2-Month Injections__ = LA Cabotegravir (600 mg): 3 mL IM + Rilpivirine (900 mg): 3 mL IM

*__Dosing for Every 1-Month Injections__ = LA Cabotegravir (400 mg): 2 mL IM + Rilpivirine (600 mg): 2 mL IM

Injections of rilpivirine and cabotegravir given as 2 separate IM injections at separate gluteal sites (opposite sites or 2 cm apart on same site)

Source: Cabotegravir-Rilpivirine Prescribing Information; Illustration: David H. Spach, MD

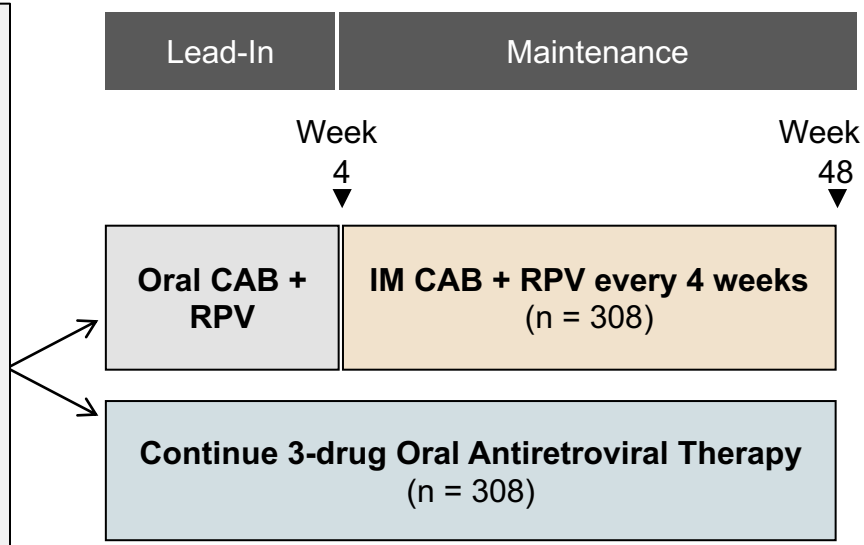
Long-Acting IM Cabotegravir and IM Rilpivirine for HIV Maintenance

ATLAS Study

National HIV Curriculum

Long-Acting IM Cabotegravir and IM Rilpivirine for HIV Maintenance
ATLAS Study: Design

- **Background**: Phase 3, randomized, open-label trial assessing IM cabotegravir plus IM rilpivirine after oral induction for adults taking a 3-drug oral antiretroviral therapy regimen
- **Inclusion Criteria**
  - Age ≥18 years
  - Taking 2 NRTIs + INSTI, NNRTI, or PI
  - Stable ARV regimen ≥6 months
  - HIV RNA <50 copies/mL ≥6 months
  - No history of virologic failure
  - No INSTI or NNRTI resistance mutations allowed, except for K103N
  - No chronic hepatitis B

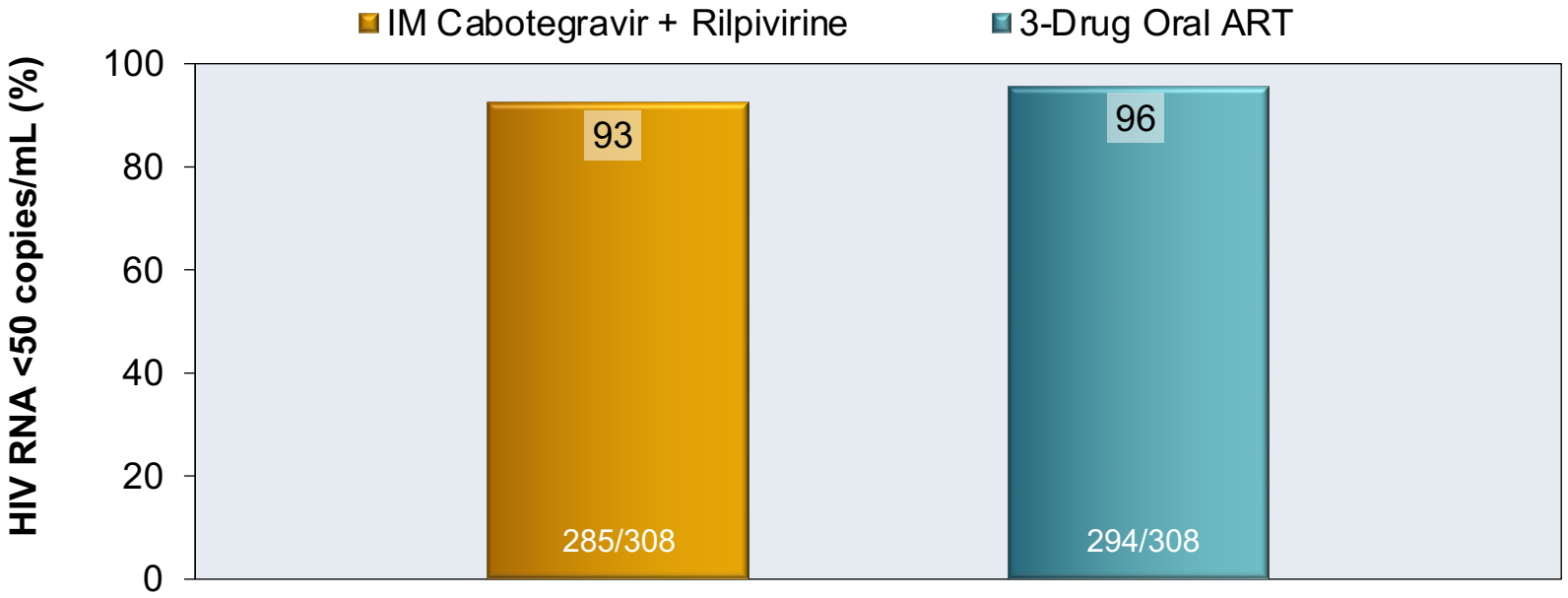


Abbreviations: CAB = cabotegravir; RPV = rilpivirine

Source: Swindells S, et al. N Engl J Med. 2020;382:1112-23.

Long-Acting IM Cabotegravir and IM Rilpivirine for HIV Maintenance
ATLAS Study: Results

Weeks 48: Virologic Response by FDA Snapshot Analysis



HIV RNA ≥50 copies/mL at 48 weeks: 2 % CAB + RPV, 1% 3-drug oral ART

Source: Swindells S, et al. N Engl J Med. 2020;382:1112-23.

Long-Acting IM Cabotegravir and IM Rilpivirine for HIV Maintenance
ATLAS Study: Results

Participants in the IM CAB-RPV arm with Viral Rebound Meeting Protocol-Defined Criteria for Genotype Resistance Testing

Country, HIV-1 Subtype	At Baseline		At Virologic Failure	
	INSTI RAMs	NNRTI RAMs	HIV RNA	INSTI RAMs
Russia, A/A1	L74I	E138E/A	25,745 copies/mL	L74I
F, France, AG	None	V108V/I, E138K	258 copies/mL	None
M, Russia, A/A1	L74I	None	1841 copies/mL	N155H, L74I

There were also 4 virologic failures in the oral ART arm; new RAMs detected included one G190S, one M184I, and one M230M/I.
Abbreviations: RAMs = resistance associated mutations

Source: Swindells S, et al. N Engl J Med. 2020;382:1112-23..

Long-Acting IM Cabotegravir and IM Rilpivirine for HIV Maintenance
ATLAS Study: Adverse Events

Injection Site Reactions (ISRs)	
Type of Reactions	**Participants (%) with Reaction**
Participants who received injections, n	303
Any reaction, n (%)	250 (81)
Pain, n (%)	231 (75)
Grade 3 pain, n, (%)	10 (3)
Pain leading to withdrawal	4 (1)
Nodule, n (%)	37 (12)
Induration, n (%)	30 (10)
Swelling, n (%)	23 (7)
Median duration of reaction, days	3
The majority of ISRs (99%) were grade 1-2; 88% resolved within 7 days.	

Source: Swindells S, et al. N Engl J Med. 2020;382:1112-23.

IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance

ATLAS-2M

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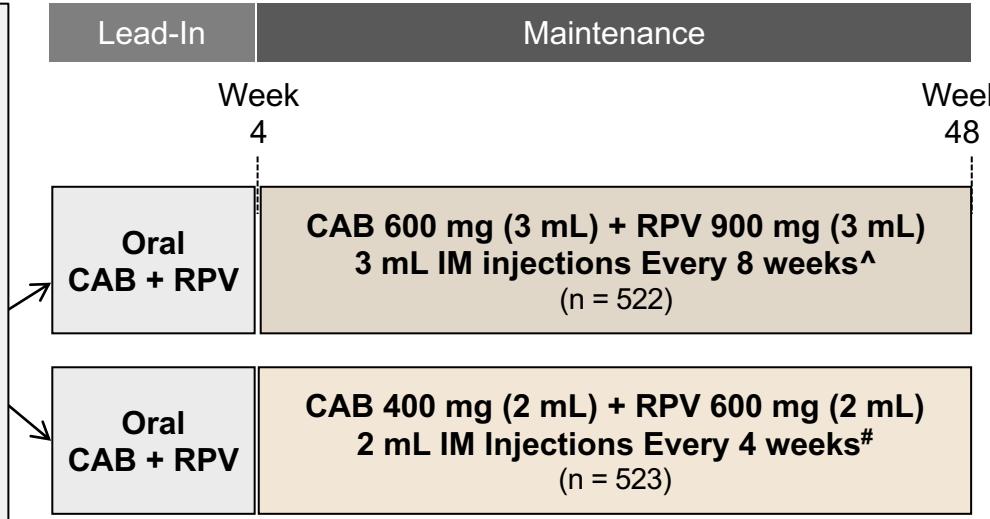
IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance
ATLAS-2M Study: Design

- **Background**: Phase 3, randomized, open-label trial assessing IM CAB plus IM RPV maintenance ART administered every 8 weeks versus every 4 weeks
- **Inclusion Criteria**
  - Age ≥18 years
  - Taking an uninterrupted first or second oral standard of care ART regimen for ≥6 months
  - HIV RNA <50 copies/mL ≥6 months at screening and >2x in prior year
  - No history of virologic failure
  - No INSTI or NNRTI resistance, except that K103N mutation allowed



*Some individuals enrolled from ATLAS trial; those already receiving IM CAB + RPV through ATLAS did not require oral lead-in for ATLAS-2M

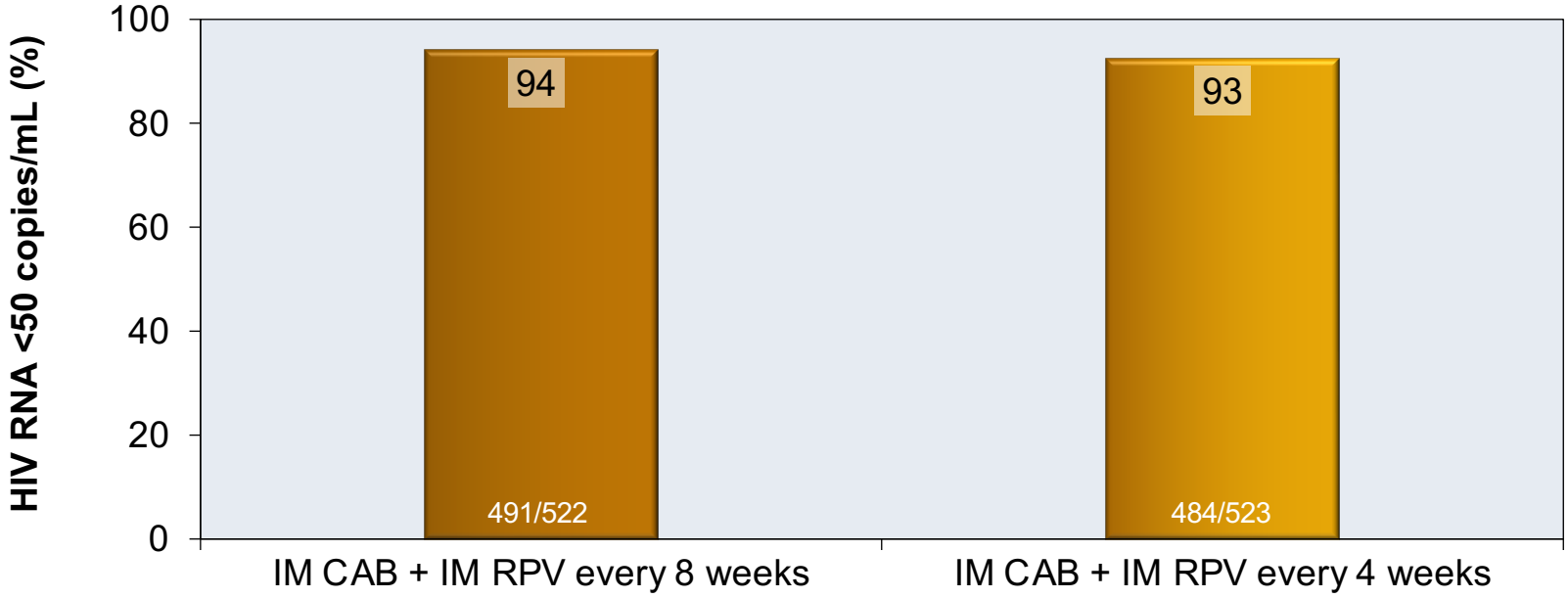
^Participants first received loading doses of CAB 600 mg (3 mL) + RPV 900 mg (3 mL) 3 mL IM injections given at study weeks 4 and 8

#Participants first received loading dose of CAB 600 mg (3 mL) + RPV 900 mg (3 mL) 3 mL IM injections given at study week 4

Source: Overton ET, et al. Lancet. 2020:396:1994-2005.

IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance
ATLAS-2M Study: Results

Weeks 48: Virologic Response by FDA Snapshot Analysis



HIV RNA ≥50 copies/mL at 48 weeks: 9/522 (2%) in q8-week arm, 5/523 (1%) in q4-week arm

Source: Overton ET, et al. Lancet. 2020:396:1994-2005.

IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance
ATLAS-2M Study: Results

Participants with Viral Rebound Meeting Protocol-Defined Criteria for Genotype Resistance Testing

	Total Number of Participants	Archived (Baseline) RPV RAMs*	Archived (Baseline) INSTI RAMs*	RPV RAMs Detected at Time of VF	INSTI RAMs Detected at Time of VF
Q8 Weeks	8	5/8	1/8	6/8	5/8
Q4 Weeks	2	0/2	0/2	1/2**	2/2

*Detected by archive (DNA) genotype

**One participant had RPV RAMs; the other an NNRTI polymorphism that reduced RPV activity >100-fold

Abbreviations: RAMs = resistance associated mutations; VF = virologic failure

Source: Overton ET, et al. Lancet. 2020:396:1994-2005.

IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance
ATLAS-2M Study: Results

Injection Site Reactions (ISRs)*		
Types of Reactions	**IM CAB + RPV Every 8 Weeks, n (%)**	**IM CAB + RPV Every 4 Weeks, n, %**
Participants who received injections, n	516	517
Any reaction, n (%)	392 (76)	390 (75)
Serious reaction, n (%)	1 (<10)	0 (0)
Reaction leading to discontinuation, n (%)	6 (1)	11 (2)
Pain, n (%)	371 (72)	363 (70)
Nodule, n (%)	54 (10)	89 (17)
Induration, n (%)	41 (8)	39 (8)
Swelling, n (%)	32 (6)	27 (5)

*The majority of ISRs (98%) were grade 1-2.

Source: Overton ET, et al. Lancet. 2020:396:1994-2005.

Long-Acting Cabotegravir-Rilpivirine Considerations if Adherence Challenges or Virologic Failure

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Long-Acting Cabotegravir-Rilpivirine (CAB-RPV) Considerations if Significant Adherence or Retention in Care Challenges

"The panel recommends **against** long-acting, intramuscular CAB and RPV in people who have detectable viral load due to suboptimal adherence to ART and who have ongoing challenges with retention in HIV care, except in a clinical trial." **(AIII)**

HHS Guidelines for Use of Antiretroviral Agents in Adults and Adolescents with HIV

Source: HHS Guidelines for Use of Antiretroviral Agents in Adults and Adolescents with HIV. Sept 21, 2022.

Long-Acting Cabotegravir-Rilpivirine (CAB-RPV) and Virologic Failure

- Guidelines previously recommended checking resistance assay(s) within 4 weeks ART stoppage
- Injectable CAB and RPV have very long half-lives
- Resistance tests now recommended with virologic failure after CAB-RPV stoppage, regardless of time since last dose

Source: HHS Guidelines for Use of Antiretroviral Agents in Adults and Adolescents with HIV. Sept 21, 2022.

Summary

- Intramuscular cabotegravir-rilpivirine (CAB-RPV) is the first approved long-acting antiretroviral treatment regimen
- Eligible patients are those taking a stable oral regimen with suppressed HIV RNA, no HBV, no CAB or RPV resistance
- Must attend visits every 1 or 2 months for injections administered by a healthcare professional
- Usage has been limited thus far due to clinical factors, insurance coverage, and logistical barriers

Acknowledgment

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